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Date: 18 November 2008



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For and on behalf of RWS Group Ltd

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The Austrian Patent Office herewith certifies that

BIOCHEMIE GmbH
of A-6250 Kundl/Tyrol
(Tyrol),

filed a patent application on the **16 April 2003**
relating to

“Organic compounds”,

and that the attached description entirely agrees with the original description filed simultaneously with this Patent Application.

Austrian Patent Office
Vienna, 11 March 2004

The President
pp
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[signature]

HRNCIR
Senior Technical Inspector

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A 586/2003

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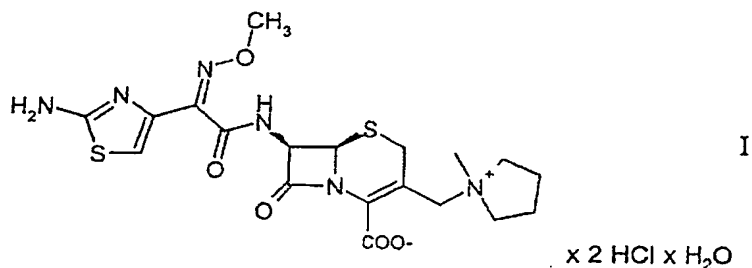
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Organic compounds

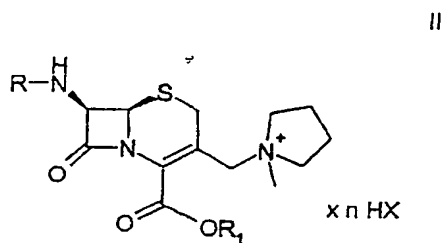
The present invention relates to the preparation of
5 1-[[(6R, 7R) -7-[[(2Z) - (2-amino-4-thiazolyl)methoxy-
imino)acetyl]amino]-2-carboxy-8-oxo-5-thia-1-
azabicyclo[4.2.0]oct-2-en-3-yl)methyl]-1-methyl-
pyrrolidinium dihydrochloride hydrate (cefepime
dihydrochloride monohydrate). Cefepime is a valuable
10 4th generation injectable cephalosporin with
antibacterial properties, see e.g. The Merck Index
Thirteenth Edition, Item 1935.



The preparation of cefepime is not simple. For example,
15 it is known that the 7-acyl side chain as the
difficult-to-obtain 2-(2-aminothiazol-4-yl)-2-methoxy-
imino-acetic acid chloride hydrochloride must be used
for the production of cefepime, in order to obtain an
active ingredient which is pure in respect of the by-
20 products anti-isomer and Δ -2 isomer.

A novel process has now been found which solves the
abovementioned problems.

25 The process comprises reaction of the β -lactam
intermediate of formula II



wherein

R_1 is a negative charge or trialkylsilyl,

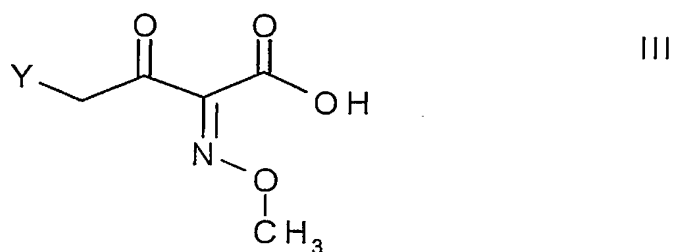
R is H or trialkylsilyl,

5 n is 0 - 2 and

X is chloride, bromide or iodide,

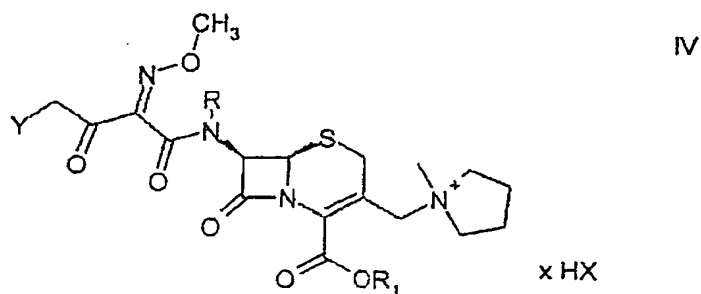
with a reactive derivative of the compound of formula

III

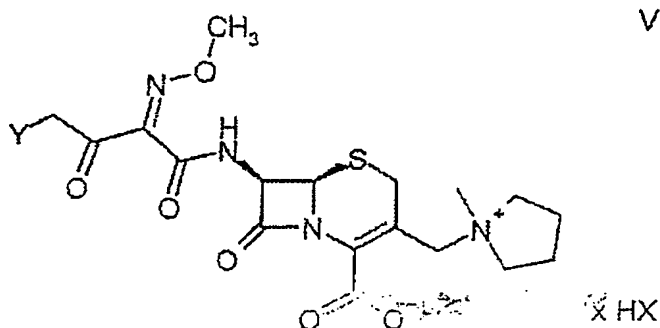


10 wherein Y is halogen,

to form a compound of formula IV



the silyl protecting groups - if present - are removed, if necessary the intermediate step of formula V



is isolated, the compound of formula IV, or the
 5 compound of formula V, is reacted with thiourea and subsequently the compound of formula I is isolated.

Y denotes chloride or bromide.

10 The compound of formula II may be used in free base form, as a mono-addition salt or as a di-addition salt with a hydrohalic acid such as hydrochloric acid, hydrobromic acid or hydriodic acid. The addition salts may additionally be present in solvated form.

15 If the silylation variant is chosen, the intermediate of formula II is obtained by methods known per se, using a silylation agent such as N,O-bis-(trimethylsilyl)-acetamide (BSA), N,O-bis-
 20 (trimethylsilyl)-trifluoroacetamide (BSTFA), N-methyl-N-trimethylsilyl-trifluoroacetamide (MSTFA) or for example hexamethyldisilazane (HMDS), in a solvent that is inert towards silylation agents, for example a nitrile, such as acetonitrile, an ether, for example
 25 tetrahydrofuran, or a chlorinated hydrocarbon, for example dichloromethane.

Subsequently, the silylated derivative of formula II is acylated with a reactive derivative of formula III, the reactive derivative being an acid chloride, acid bromide or active ester, for example a S-mercapto-
5 benzothiazolyl ester, optionally in the presence of an auxiliary base such as a tertiary alkylamine.

The compound of formula IV is subsequently desilylated with the assistance of a protic reagent, for example
10 water or an alcohol, and then the compound of formula IV is reacted with thiourea in an aqueous or organic-aqueous medium. The title compound is subsequently crystallised, if necessary after separating the organic solvent, and where appropriate after removing any salt
15 that is present, for example after treatment using anion exchangers by methods known per se after adding hydrochloric acid from an aqueous acetonitrile solution.

An alternative is to work in an aqueous or aqueous-
20 organic system, for example in a one-phase system consisting of water and a water-miscible solvent, for example a ketone, such as acetone, a nitrile, such as acetonitrile, or an ether, such as tetrahydrofuran, or in a two-phase system, for example in a combination of
25 an ester of acetic acid, for example ethyl acetate, a chlorinated hydrocarbon, for example dichloromethane, or for example an aromatic, for example toluene, and the compound of formula II is optionally released from its mono- or di-addition salt with the assistance of a
30 base, for example caustic soda solution or caustic potash solution, a sodium or potassium hydrogen carbonate or alkali carbonate, or by methods known per se using an ion exchanger, and subsequently the compound of formula II is acylated with a reactive
35 derivative of formula III. After the acylation reaction has taken place, thiourea is added, and optionally after separating the organic solvent, the title

compound is isolated by methods known per se by adding acetone from an aqueous/acetic solution.

If desired, it is possible to isolate the compound of formula IV, as an addition salt with a hydrohalic acid, for example as the hydrochloride. Here, the reaction sequence preferably starts with an acid addition salt of the compound of formula II, via the silylation route. By adding small amounts of protic solvent, for example water or an alcohol, to the compound of formula IV wherein R₁ and R preferably denote trialkylsilyl, the silyl groups are removed, and the halide present in the system enables direct crystallisation of the compound of formula V to take place. The preferred mono-addition salt is the monohydrochloride in crystalline form. In order to produce this, the compound of formula II is preferably used as the mono- or di-hydrochloride addition salt, and the preferred solvents for crystallisation are acetonitrile in combination with isopropanol.

The examples below elucidate the invention in more detail.

Example 1

Preparation of 1-[[[(6R,7R)-7-[[[(2Z)-(4-chloro-2-methoxyimino-3-oxo-butyryl]amino]-2-carboxy-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-en-3-yl]methyl]-1-methyl-pyrrolidinium hydrochloride

1.55 g of N,O-bis(trimethylsilyl)acetamide are added dropwise at room temperature to a suspension of 0.835 g of NMP-ACA.2HCl in 10.5 ml of acetonitrile. After stirring for 25 mins at room temperature, the solution obtained is cooled to -35°C. At this temperature, a solution of 4-chloro-2-methoxyimino-3-oxo-butyryl chloride in acetonitrile (for preparation see example

1a), which has been cooled to -20°C, is added. After stirring for 1 hour in a cooling bath at -35°C, 2 ml of isopropanol are added dropwise. The resulting suspension is heated to 0°C and stirred for 1 hour in an ice bath. The suspension is then filtered. The filter cake is washed with acetonitrile. After drying in a vacuum at room temperature, 1.42 g of product is obtained as a white crystalline powder.

¹H-NMR spectrum (DMSO-d₆, δ in ppm)
1.957 - 1.690 (m, 2H, pyrrolidinyl-H); 2.943 (s, 3 H, N-CH₃); 3.371 - 3.701 (m, 5 H, pyrrolidinyl-H, S-CH₂); 3.866 (1 H, J = 10.0 Hz, S-CH₂); 4.060 (s, 3 H, OCH₃); 4.329 and 4.597 (ABq, 2 H, J = 13.7 Hz, -CH₂-N); 4.846 (s, 2 H, CH₂Cl); 5.322 (d, 1 H, 5.1 Hz, H₆); 5.884 (dd, 1H, J = 8.4 Hz, J = 5.1 Hz, H₇); 9.555 (d, 1H, NH)

Example 1a

Preparation of 4-chloro-2-methoxyimino-3-oxo-butyryl chloride

A solution of 0.488 g of 4-chloro-2-methoxyiminobutyric acid in 8.0 ml of acetonitrile is mixed at -20°C with 0.353 g of chloromethylene iminium chloride (Vilsmeier reagent) and stirred for 1 hour at -20°C.

Example 2

Preparation of 1-[[[(6R,7R)-7-[[[(2Z)-(2-amino-4-thiazolyl)methoxyimino)acetyl]amino]-2-carboxy-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-en-3-yl]methyl]-1-methylpyrrolidinium dihydrochloride hydrate (cefepime dihydrochloride monohydrate)

0.990 g of 1-[[[(6R,7R)-7-[[[(2Z)-(4-chloro-2-methoxyimino-3-oxo-butyryl]amino)-2-carboxy-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-en-3-yl]methyl]-1-methylpyrrolidinium hydrochloride are added at 4°C to a

solution of 0.152 g of thiourea in 5 ml of H₂O. The pH of the suspension is adjusted to pH 6.0 with ion exchanger LA-2 and maintained in the pH range of 5.5 to 6.0 by adding LA-2 dropwise. After stirring for 8.5
5 hours at 2 to 4°C, the reaction mixture is washed with 10 ml of methylene chloride. After phase separation, the aqueous phase is washed a second time with 10 ml of methylene chloride. The organic phases are combined and then extracted with 3 ml of H₂O. The aqueous phases are
10 combined and mixed with 0.20 g of activated carbon. After stirring for 10 minutes, the carbon suspension is filtered. The carbon cake is washed with 1.5 ml of H₂O. The filtrate and washing water are combined, acidified with 6 m HCl to pH 0.6 and mixed with 50 ml of acetone.
15 After adding seed crystals, stirring is effected for 15 minutes at room temperature, and then 50 ml of acetone is added dropwise over the course of 1 hour. The crystal suspension obtained is cooled to 0°C. After stirring for 1 hour in an ice bath, the suspension is
20 filtered and the filter cake is washed with acetone. After drying in a vacuum at room temperature, 0.561 g of the title compound are obtained in the form of a white crystalline powder.

25 HPLC purity: 99.6 area %

Example 3

Preparation of 1-[[[(6R,7R)-7-[[[(2Z)-(2-amino-4-thiazolyl)methoxyimino)acetyl]amino]-2-carboxy-8-oxo-5-
30 thia-1-azabicyclo[4.2.0]oct-2-en-3-yl)methyl]-1-methylpyrrolidinium dihydrochloride hydrate (cefepime dihydrochloride monohydrate)

1.55 g of N,O-bis(trimethylsilyl)acetamide are added
35 dropwise at 1°C to a suspension of 0.835 g of pyrrolidinium-1-[(7-amino-2-carboxy-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-en-yl)methyl]-dihydrochloride in

10.5 ml of acetonitrile. After stirring for 45 mins in an ice bath, the solution obtained is cooled to -35°C. At this temperature, a solution of 4-chloro-2-methoxy-imino-3-oxo-butyryl chloride (for preparation see
5 example 1a), which has been cooled to -20°C, is added. After stirring for 1 hour in a cooling bath at -35°C, 2 ml of H₂O are added dropwise. After stirring for 10 minutes at -35°C, 0.38 g of thiourea are added. The reaction mixture is subsequently heated to 0°C and the
10 pH is adjusted to 6.0 by adding ion exchanger LA-2, and is maintained at this pH. After stirring for 2 hours in an ice bath, the 2-phase reaction mixture obtained is mixed with 2 ml of H₂O. After stirring for a further 16 hours at 0 to 4°C, the pH is acidified to pH 0.60 with
15 6 m HCl. After adding 50 ml of methylene chloride, the phases are separated. The methylene chloride phase is then extracted with 3 ml of H₂O. The aqueous phases are combined and mixed with 0.10 g of activated carbon. After stirring for 10 minutes, the activated carbon
20 suspension is filtered. The carbon cake is washed with 1 ml of H₂O. The filtrate and washing water are combined and diluted with 30 ml of acetone. After adding seed crystals, stirring is effected for 30 minutes at room temperature. Then, 20 ml of acetone are added dropwise
25 to the resulting crystal suspension over the course of 30 minutes. The suspension is cooled to 0°C. After stirring for 1 hour in an ice bath, the product is isolated and the filter cake is washed with acetone. After drying in a vacuum at room temperature, 0.742 g
30 of the title compound are obtained in the form of a white crystalline powder.

HPLC purity: 99.5 area %

35 Example 4

Preparation of 1-[[[(6R,7R)-7-[[[(2Z)-(2-amino-4-thiazolyl)methoxyimino)acetyl]amino]-2-carboxy-8-oxo-5-

thia-1-azabicyclo[4.2.0]oct-2-en-3-yl)methyl]-1-methyl-pyrrolidinium dihydrochloride hydrate (cefepime dihydrochloride monohydrate)

5 1.706 g of pyrrolidinium-1-[(7-amino-2-carboxy-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-en-yl)methyl]-dihydrochloride are added to a mixture of 10 ml of H₂O and 5 ml of methylene chloride, and the pH is adjusted to 6.50 by adding ion exchanger LA-2. The 2-phase mixture is
10 cooled in an ice bath to 1°C. At this temperature, a solution of 4-chloro-2-methoxyimino-3-oxo-butyryl chloride, produced from 1.464 g of 4-chloro-2-methoxyimino-3-oxo-butyric acid (see example 1a), which has been cooled to -20°C, is added dropwise over the
15 course of 1 hour, and the pH is maintained in the range of 6.0 to 6.5 by adding base LA-2. After stirring for 15 minutes in an ice bath, 0.76 g of thiourea are added and stirring is effected for 16 hours at 2-4°C. The pH is maintained in the range of 5.5 to 6.0 with LA-2. The
20 reaction mixture is subsequently diluted with 100 ml of methylene chloride. After phase separation, the aqueous phase is washed with 50 ml of methylene chloride. The methylene chloride phases are combined and then extracted with 3 ml of H₂O. The product-containing
25 aqueous phases are combined and mixed with 0.20 g of activated carbon. After stirring for 10 minutes, the activated carbon suspension is filtered. The carbon cake is washed with 1.5 ml of H₂O. The filtrate and washing water are combined and diluted with 60 ml of
30 acetone. After adding seed crystals, stirring is effected for 30 minutes at room temperature. Then, 40 ml of acetone are added dropwise to the resulting crystal suspension over the course of 30 minutes. The suspension is cooled to 0°C. After stirring for 1 hour
35 in an ice bath, the product is isolated and the filter cake is washed with acetone. After drying in a vacuum

Case G-33166/P1/BCK9938

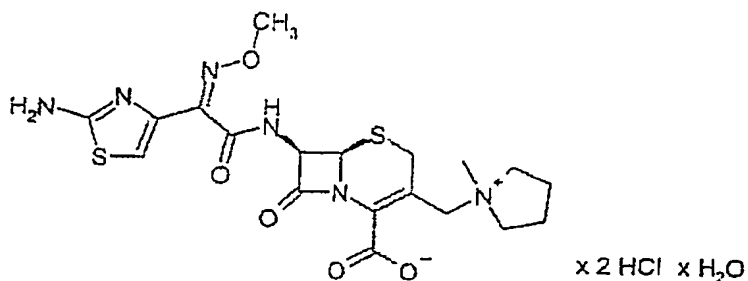
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at room temperature, 1.236 g of the title compound are obtained in the form of a white crystalline powder.

HPLC purity: 90.0 area %

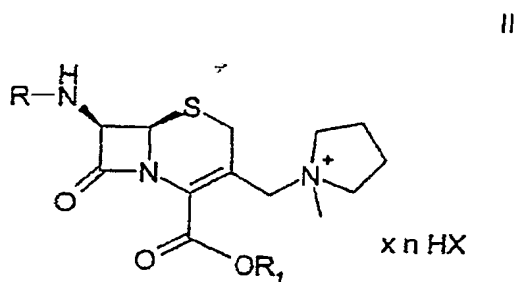
Claims

1. A process for producing a compound of formula I



5 .

wherein a compound of formula II



wherein

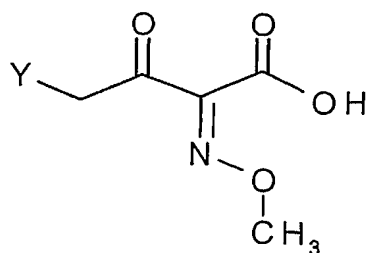
R₁ is a negative charge or a trialkylsilyl group,

10 R is hydrogen or a trialkylsilyl group,

n is 0 - 2 and

X signifies chloride, bromide or iodide

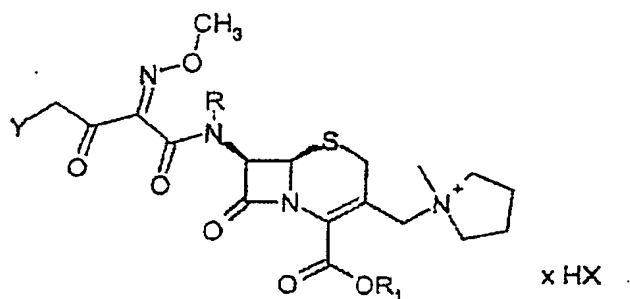
is reacted with a reactive derivative of formula III



III

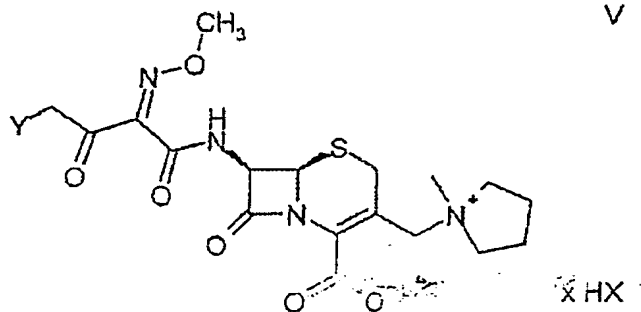
wherein Y signifies halogen, to form a compound of formula IV

IV



- 5 the silyl protecting groups, if present, are removed, or the compound of formula IV as the acid addition salt of formula V is isolated and the compound of formula IV

V



- 10 or the compound of formula V is cyclised with thiourea, and subsequently the compound of formula I is isolated.

2. A process as claimed in claim 1, wherein the compound of formula II is produced from its mono- or di-hydrogen halide adducts.

5 3. A process as claimed in claim 1 or 2, wherein pyrrolidinium-1-[(7-amino-2-carboxy-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-en-yl)methyl]-iodide monohydrate is used.

10 4. A process as claimed in claim 1 or 2, wherein pyrrolidinium-1-[(7-amino-2-carboxy-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-en-yl)methyl]-chloride is used, optionally in solvated form.

15 5. A process as claimed in claim 1 or 2, wherein pyrrolidinium-1-[(7-amino-2-carboxy-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-en-yl)methyl]-dihydrochloride is used, optionally in solvated form.

20 6. A compound of formula V, wherein Y and X are Cl.

7. A compound as claimed in claim 6 in crystalline form.

25 8. A process as claimed in claim 1, wherein 4-chloro-2-methoxyimino-3-oxo-butyryl chloride is used as the reactive derivative of formula III.

30 9. A process as claimed in any of claims 1 to 5 or 8, wherein prior to crystallisation of the compound of formula I, any bromide or iodide ions that may be present are removed by ion exchanger.

Biochemie GmbH